REMARKS

The Office Action

Claims 1-32 were pending in this application. With this reply, claims 1-11 and 16-21 have been cancelled, and claims 33-37 have been added. The status of claims 14 and 23-28 have been changed from 'withdrawn' to 'previously presented' or 'original' to clarify that these claims fall within the restriction group presently under consideration by the Office. Accordingly, with this reply claims 12-15 and 22-35 are pending and under consideration. Claims 12-15, 19-23, 25, and 28-32 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. Claims 12-15, 19-23, 25, and 28-32 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 12-15, 19-23, 25, and 28-32 stand rejected under 35 U.S.C. § 102(b) for lack of novelty.

Rejection under 35 U.S.C. § 112, first paragraph, for lack of written description

Claims 12-15, 19-23, 25, and 28-32 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. The Office has issued a two-part rejection. As a first basis for this rejection, the Office states "though the claims may recite some functional characteristics, the claims lack written description because there is no correlation between function and structure of the compounds beyond compounds disclosed in the examples in the specification" (Office Action at page 7). As a second basis for this rejection, the Office states "the specification lack[s] sufficient variety of

species to reflect [the] variance in the genus since the specification does not provide examples of methods of treating [using] ... a representative number of corticosteroid conjugates..." (Office Action at page 7).

Applicant has addressed these rejections by amending claim 12 and with the following remarks.

The invention as claimed features a method for treating an autoimmune or inflammatory condition by administering a peripherally acting corticosteroid conjugate. The corticosteroid conjugate has three characteristic components: a corticosteroid covalently tethered, via a linker, to a group that is bulky or charged. The function of the bulky or charged group is solely to increase the size or charge of the corticosteroid sufficiently to inhibit passage across the blood-brain barrier.

As amended, claim 12, and dependent claims 13-15 and 22-33, are limited to corticosteroid conjugates in which the corticosteroid is a compound of formula I attached to a charged or bulky group via a linker described by formula III. As noted above, the bulky or charged group is selected to modify the pharmacokinetic profile such that the corticosteroid conjugate has reduced CNS activity in comparison its parent corticosteroid. The specification provides clear and adequate instructions with respect to the selection of a group that provides the mere bulk or charge (see, for example, the specification from page 19, line 4, to page 21, line 12). Applicant asserts that the structural limitations now incorporated into claim 12 are sufficient to provide one of skill in the art a written

description of the claimed genus.

With respect to the use of the corticosteroid conjugates of the invention, Applicants note that these compounds are derived from parent corticosteroids which are already known to be useful for the treatment of autoimmune and inflammatory conditions. For example, Jacobs et al., *Ann. Rheum. Dis.* 60:61 (2001) (Exhibit A, included herewith) describes the use of corticosteroid therapy for the treatment of rheumatoid arthritis, Potsma et al., *Eur. Respir. J.* 17:1083 (2001) (Exhibit B, included herewith) describes the use of corticosteroid therapy for the treatment of asthma, Bertz et al., *Bone Marrow Transplantation*, 24:1185 (1999) (Exhibit C, included herewith) describes the use of corticosteroid therapy for the treatment of graft versus host disease, and Campieri et al., *Gut* 1997; 41: 209–214 (Exhibit D, included herewith) describes the use of corticosteroid therapy for the treatment of Crohn's disease.

The prior art provides significant teaching regarding the use of corticosteroids, compounds belonging to the same structural and functional class as the corticosteroid conjugates used in the claimed methods. Applicants submit that, given the teaching of the specification and the level of skill known in the art at the time the present application was filed, one skilled in the art could instantly recognize that the Applicant was in possession of how to use the compounds recited in the claimed methods and throughout the full scope of the claims.

In view of the amendment to claim 12 and the remarks above, Applicant requests

withdrawal of the rejection for lack of written description.

Rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement

Claims 12-15, 19-23, 25, and 28-32 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. As a basis for this rejection, the Office states that the term "treating," as defined in the specification, includes preventing disease, which is beyond the scope of the invention. Applicant has addressed this rejection by amending claim 12 and with the following remarks.

As amended, claim 12, and dependent claims 13-15 and 22-33, are limited to a method of "treating for therapeutic purposes a mammal suffering from an autoimmune or inflammatory condition." Thus, the instant claims, as amended, do not encompass the use of corticosteroid conjugates for the prevention of disease.

In view of the amendment to claim 12 and the remarks above, Applicant requests withdrawal of the rejection for lack of enablement.

Rejection under 35 U.S.C. § 102(b)

Claims 12, 13, 15, 19-23, and 29-30 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Zhang et al., *J. Pharm. Sci.* 2001 (hereafter "Zhang"). As a basis for this rejection, the Office states the Examiner is not persuaded by Applicant's arguments because "the limitations (i), (ii) and (iii) appear after a wherein clause" and so may be

considered optional language that does not require reading these limitations into the claims. Applicant has addressed this rejection by amending claim 12 and with the following remarks.

Claim 12 has been amended to remove the wherein clause preceding limitations (i), (ii), and (iii). As amended, claim 12, and dependent claims 13-15 and 22-33, are limited to corticosteroid conjugates (i) having anti-inflammatory activity *in vivo*, (ii) having reduced activity in the central nervous system in comparison to said corticosteroid without said group, and (iii) being resistant to *in vivo* cleavage, such that *in vivo* less than 10% of the administered corticosteroid conjugate is cleaved, separating said corticosteroid from said group, prior to excretion. For reasons of record, limitations (i), (ii), and (iii) distinguish Zhang, which describes a prodrug that is cleaved *in vivo*, from the corticosteroid conjugates of the invention.

In view of the amendment to claim 12 and the remarks above, Applicant requests withdrawal of the rejection for lack of novelty.

Support for the Amendment to claim 12 and new claims 33-37

Claim 12 has been amended to include the limitation that the corticosteroid conjugate is (i) a corticosteroid of formula I, (ii) attached via a linker to a charged or bulky group, and (iii) the linker is described by formula III. Support for these limitations are found in claims 2-4 as originally filed and found in the specification from page 3, line

9, to page 4, line 18. Claim 12 has also been amended to include the limitation "treating for therapeutic purposes." Support for this limitation is found in the specification at page 9, lines 3-10.

Support for the parent corticosteroid being selected from beclomethasone, budesonide, prednisolone, prednisone, and triamcinolone, as recited in new claim 33, is found in the specification from page 11, line 1, to page 14, line 5.

Support for the corticosteroid conjugates of formulas V, VI, VII, and VIII, as recited in new claims 34-37, is found in the specification from page 21, line 23, to page 22, line 11.

No new matter has been added with these amendments.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and such action is respectfully requested. To expedite prosecution applicants request a telephonic interview with the Examiner to discuss any remaining rejections. The Examiner is invited to call the undersigned at 617-428-0200.

Enclosed is a petition to extend the period for replying for three months, to and including Monday September 24, 2007, as Saturday September 22, 2007, fell on a weekend. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 9-24-07

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CONCISE REPORTS

Short term effects of corticosteroid pulse treatment on disease activity and the wellbeing of patients with active rheumatoid arthritis

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Abstract

***Objective*—To investigate the short term effects of corticosteroid pulse treatment (CPT) on disease activity, functional ability, and psychological wellbeing of patients with active rheumatoid arthritis (RA).**

***Methods*—Of 66 consecutive patients with active RA admitted for CPT, erythrocyte sedimentation rate, C reactive protein level, haemoglobin concentration, platelet count, duration of early morning stiffness, a joint score, and grip strength were assessed before and after CPT. Additionally, a health status questionnaire was administered. Effects of CPT were expressed as before to after intervention effect sizes and, to place them in perspective, compared with the (long term) effect sizes of disease modifying antirheumatic drug (DMARD) treatment in a historical contrast group of patients with early RA.**

***Results*—Statistically significant improvement from baseline in disease activity, physical functioning, and psychological wellbeing after CPT was seen, with moderate to large effect sizes, resembling the effects seen after DMARD treatment. Neither depression nor psychosis occurred during and after CPT.**

***Conclusion*—Qualitatively and quantitatively the short term effects of CPT in patients with active established RA on various dimensions of health status resemble the long term effects of conventional DMARD treatment in patients with early RA. Psychological disorders do not seem to be common short term side effects of CPT in patients with active RA.**

(*Ann Rheum Dis* 2001;60:61–64)

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Recently published results of trials with low and high dose corticosteroid treatment (CT) are a reflection of renewed interest in this topic.[1 2] Intravenous administration of high doses of corticosteroids (corticosteroid pulse therapy, CPT) is used in rheumatoid arthritis (RA) to suppress inflammation—for example, to bridge the lag time of recently prescribed disease modifying antirheumatic drugs (DMARDs), and to treat extra-articular complications such as vasculitis.[3] With CPT the serious long term side effects of chronic oral corticosteroid treatment—with the exception of osteonecrosis—are avoided; short term side effect are usually mild.[3] CPT may have less effect on bone resorption than continuous oral CT.[4 5] The effect of CPT on clinical measures such as morning stiffness, pain, grip strength, and joint score varies in general between four and 10 weeks, but patients with long term remission of RA have been described.[3]

In various diseases the percentage of patients developing psychiatric symptoms (depression, hypomania, mania, or psychosis) during CT, especially given in high doses, has been reported to range from 3 to 75%.[6–8] In patients with RA, quantitative data on the effect of CPT or high dose oral CT on psychological wellbeing and quality of life are sparse. This study aimed at quantifying the short term effect of CPT on disease activity and self reported measures of psychosocial wellbeing and physical functioning of patients with active RA.

Patients and methods

Over a period of five years all consecutive patients with active RA, admitted to the rheumatology ward of the University Medical Center, Utrecht, to undergo CPT to bridge the lag time of a newly started DMARD, were included in this study after informed consent. If a patient was admitted more than once for CPT in this period of five years, only the first admission was used. None of the 66 patients receiving CPT (CPT group) refused to participate. Active disease was defined as the presence of at least two of the following three criteria: Thompson joint score >10,[9] erythrocyte sedimentation rate (ESR) ≥28 mm/1st h, and early morning stiffness ≥1 hour. Each CPT regimen comprised three doses of 200 mg dexamethasone (each dose 1000 mg methylprednisolone equivalent), given through an intravenous infusion on alternate days over a five day period.

Table 1 Short term effects of corticoid pulse treatment (CPT) and long term effects of conventional disease modifying antirheumatic drug (DMARD) treatment‡. Results are given as means (SD) and effect sizes (ES)¶

	CPT group (n=66)			*DMARD contrast group (n=181)*		
	Before	*After*	*ES*	*ES*	*Before*	*After*
ESR† (mm/1st h)	68 (33)	38 (27)	1.01*****	0.60*****	41 (28)	26 (24)
CRP† (mg/l)	57 (46)	16 (32)	1.05*****	0.75*****	34 (42)	11 (18)
Haemoglobin (mmol/l)	7.5 (1.0)	7.6 (1.0)	0.09	0.31****	7.9 (0.9)	8.2 (0.9)
Platelets ($\times 10^9$/l)	358 (128)	353 (125)	0.04	0.45*****	344 (120)	292 (103)
EMS† (min)	126 (110)	34 (43)	1.17*****	0.54*****	111 (153)	44 (94)
Joint score† (0-534)	355 (137)	244 (144)	0.80*****	1.01*****	142 (100)	52 (79)
Grip strength† (kPa)	8 (11)	15 (14)	0.56*****	0.40*****	30 (22)	40 (25)
IRGL scales:						
Mobility (7-28)	12.1 (3.5)	13.4 (4.0)	0.35*	0.45*****	17.8 (6.2)	20.6 (6.0)
Self care (8-32)	14.9 (5.2)	17.8 (5.5)	0.55****	0.51*****	22.6 (6.2)	25.7 (6.1)
Pain (6-25)	22.0 (3.0)	12.8 (5.3)	2.22*****	1.07*****	18.5 (4.6)	13.2 (5.4)
Depressed mood (0-24)	5.9 (5.2)	2.2 (4.1)	0.77*****	0.46*****	5.3 (4.9)	3.3 (3.6)
Cheerful mood (0-24)	7.9 (4.2)	11.8 (3.5)	0.99*****	0.50*****	9.6 (4.6)	11.9 (4.3)
Anxiety (10-40)	21.9 (5.0)	19.2 (4.9)	0.54*****	0.38*****	20.4 (6.3)	18.1 (5.9)
Potential support (5-20)	16.2 (4.1)	15.8 (4.2)	0.10	0.11	16.8 (3.6)	16.4 (3.7)
Actual support (3-12)	6.5 (1.7)	6.5 (1.9)	0.00	0.04	6.6 (1.8)	6.5 (1.8)
Impact on eating/sleeping (2-8)	4.3 (1.3)	3.8 (1.2)	0.44***	0.46*****	4.2 (1.6)	3.5 (1.5)
Impact on relationships (2-8)	3.4 (1.8)	3.2 (1.6)	0.09	0.08	3.1 (1.6)	3.3 (1.8)

†ESR = erythrocyte sedimentation rate, Westergren method, range 0–140; CRP = C reactive protein, range 0–∞; EMS = early morning stiffness; joint score = according to Thompson; grip strength = with Martin vigorimeter.
‡Second assessment (denoted "after" in the heading of the table) at 1.3 (SD 1.0) weeks for the CPT group and 12 months in the DMARD contrast group.
¶Statistical significance levels of changes from baseline: *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001; *****p<0.00001; all statistically significant changes denote improvement.

At admission and 1–2 days before discharge from the hospital, the following variables were assessed: ESR, C reactive protein level (CRP), haemoglobin concentration, platelet count, duration of early morning stiffness, the joint score according to Thompson, and grip strength (assessed in kPa, Martin vigorimeter). In addition, the IRGL questionnaire (Impact of Rheumatic diseases on General health and Lifestyle) was administered. The IRGL is a health status questionnaire, developed from the Arthritis Impact Measurement Scales 1 (AIMS1), assessing physical, psychological, and social functioning as well as the impact of the disease on daily life.[10] The scales of the IRGL differ in their individual ranges and are expressed in the original direction—for example, high values on the scale pain, and low values on the scales mobility and self care indicate a poor health status. Side effects, including psychosis or depression, were recorded by the doctor at clinical observation.

To put the (short term) effects and effect sizes of CPT in perspective we compared them with the (long term) effects and effect sizes of DMARD treatment in a historical contrast group of 181 outpatients with recent onset RA, evaluated at the start and after one year of treatment with a DMARD (starting with hydroxychloroquine, 400 mg/day or aurothioglucose, 50 mg/week or oral methotrexate, 7.5–15 mg/week).[11] The two groups cannot be compared directly, obviously, because the selection criteria and the periods between assessments differ. In the DMARD contrast group, the same variables as in the CPT group were assessed.

STATISTICAL ANALYSIS

Means and standard deviations (SD) of baseline scores, scores after treatment, and effect sizes (ES) of the variables were calculated. The larger the ES, the larger the effect; an ES of 0.20 denotes a small, of 0.50 a moderate, and of 0.80 a large effect.[12] Within-group changes in the variables were tested for statistical significance with paired Student's t tests where there was a normal distribution, and Wilcoxon signed rank tests for differences in medians where the distribution was not normal.

To investigate the number of patients with clinically relevant improvement on each variable in the CPT group, for each outcome variable the numbers of patients with deterioration, no clinically relevant change, or improvement from baseline were calculated. Deterioration was defined as a deterioration in a variable >33% and no clinically relevant change as a change of ≤33%; an improvement in a variable >33% was defined as a clinically relevant improvement.[13] Also, the numbers of patients with a clinically relevant overall response to treatment (individual patient's improvement) in the CPT and the DMARD contrast group were calculated. A clinically relevant overall response was defined as at least 20% improvement in joint score and at least 20% improvement in three of the four following end points: (*a*) ESR or CRP; (*b*) grip strength; (*c*) early morning stiffness; (*d*) pain.

All tests were two sided; a p value <0.05 was considered to be significant. The statistical analyses were performed with the Number Cruncher Statistical system (NCSS) and SPSS/PC+ statistical packages (NCSS, Kaysville, Utah; SPSS Inc, Chicago, Illinois).

Results

The mean ages (SD) in the CPT group and DMARD contrast group were 58 (13) and 57 (14) years, respectively; duration of RA in the CPT group was 12 (10) years. The mean duration (SD) of admission for the CPT group was 1.3 (1.0) weeks and the median time period between assessments eight days; 66% of the patients in this group had used three or more DMARDs at the time of admission.

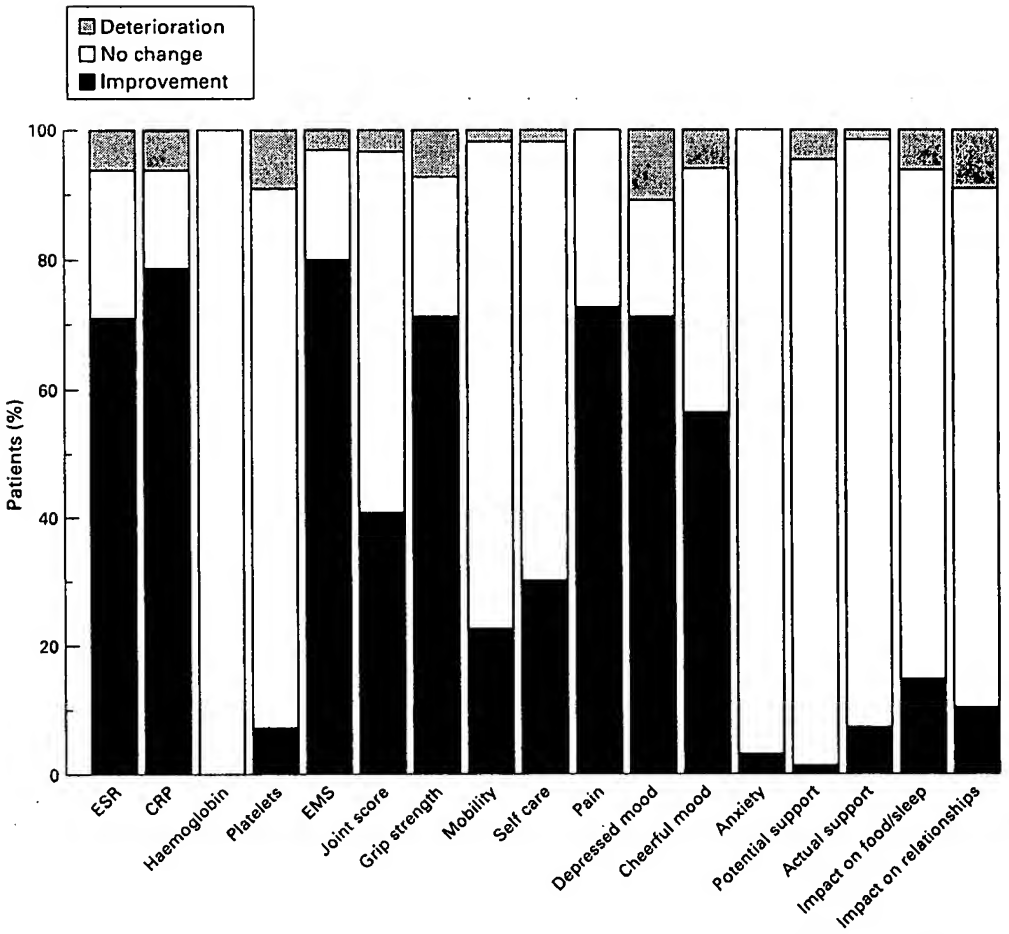

Figure 1 Percentages of patients with deterioration, no change, or improvement for each variable CPT group (n=66), stacked bars. Improvement on platelets is a decrease in count.

Table 1 shows the means (SD) of the variable measures at the start and second assessment in both groups, together with the corresponding ES. Variables of disease activity and psychological wellbeing, in general, show a large ES and those reflecting functional ability a moderate ES. Figure 1 shows the percentages of patients in the CPT group with deterioration, no clinically relevant change, or improvement from baseline for each individual variable. More than 50% of patients improved by 33% or more in ESR, CRP, early morning stiffness, grip strength, pain, depressed mood, and cheerful mood. For the other variables, >50% of the patients showed no clinically relevant change. In seven patients their depressed mood deteriorated; however, the mean score before treatment for these patients was 1 (range 0–3) and the mean score after treatment 4 (range 2–7) on a scale ranging from 0 (no depression) to 24 (severe depression). These deteriorations thus were small changes in the lower, non-depressive range of the scale. Clinical observation in the CPT group disclosed in many patients a sense of euphoria after treatment, but no cases of psychosis or depression. Common short term complications of CPT encountered were increase in blood pressure, hyperglycaemia, and facial flushing, as reported earlier.[1]

In the CPT group the percentage of patients with a clinically relevant overall response to treatment (individual patient's improvement) was 53; in the DMARD contrast group the percentage was exactly the same.

Discussion

This study aimed at qualitatively and quantitatively analysing the short term effect of CPT on health status among patients with active RA; the results may be relevant also for treatment strategies with high dose oral CT.[2] After CPT, clinically relevant changes are found for the same variables that show clinically relevant changes with DMARD treatment in three domains of health status: disease activity, physical functioning, and psychological well-being. In the CPT group the percentage of patients with a clinically relevant overall response to treatment was the same as in the DMARD contrast group.

In the CPT group, the IRGL showed enhanced psychological wellbeing, and clinical observation disclosed no depression or psychosis. So depression and psychosis do not seem to be common short term side effects of CPT in patients with active established RA. Psychological side effects generally begin during the first weeks after the start of treatment[6–8]; however, our results do not rule out the possibility of psychological disturbances later on. The incidence of depression and psychosis due to CPT in patients with active RA who improve within days may be different from the (high)

incidence of psychological disorders in patients with other diseases—for example, in patients with nephritis, in whom no short term beneficial effects occur, or in whom short term negative effects of corticosteroids may even predominate, or in patients, in whom psychological disturbances may be part of the disease—for example, systemic lupus erythematosus.

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Eur Respir J 2001; 17: 1083–1088
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Exhibit B

European Respiratory Journal
ISSN 0903-1936

Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening

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Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening. D.S. Postma, C. Sevette, Y. Martinat, N. Schlösser, J. Aumann, H. Kafé. ©ERS Journals Ltd 2001.

ABSTRACT: The study addressed the question whether the novel inhaled prodrug corticosteroid ciclesonide is equally effective when inhaled in the morning compared to the evening.

For this purpose a double-blind, randomized, parallel group study was initiated in which 209 asthmatic patients (forced expiratory volume in one second = 50–90% predicted) inhaled either 200 µg ciclesonide in the morning or in the evening, for 8 weeks. Efficacy was assessed by means of spirometry as well as daily recordings of morning and evening peak expiratory flow (PEF), symptoms and use of rescue medication. The 24-h urinary cortisol excretion was measured to evaluate any effect on hypothalamic-pituitary-adrenol axis.

Ciclesonide significantly improved asthma control. Morning and evening administration was shown to be equally effective for the different spirometry variables, evening PEF, symptoms, use of rescue medication and number of asthma exacerbations. Regarding morning PEF, the improvements after evening dosing were more prominent and equivalence of morning and evening administration could not be demonstrated. No relevant influence on cortisol excretion was found.

Overall, the study indicates that ciclesonide can be given either in the morning or in the evening to meet the patients' preference and individual medical needs, although evening administration may lead to a more pronounced improvement in morning peak expiratory flow.

Eur Respir J 2001; 17: 1083–1088.

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once daily

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Inhaled corticosteroids have become the mainstay of therapy for patients with asthma. However, as with other inhaled or oral asthma drugs, compliance to inhaled steroids is often poor [1]. Among the manifold reasons underlying noncompliance, complicated regimens and dosing frequency are considered to be significant factors. Initially, inhaled steroids were recommended to be used four-times a day. Although such a regimen might be more effective than twice-daily dosing [2], in daily life higher compliance with a twice-daily regimen might well compensate reduced efficacy [3]. Meanwhile numerous studies have shown that in the majority of patients a twice-daily schedule can effectively control asthma and this is presently the standard scheme. Additionally, it was suggested that decreasing the dosing frequency to once daily might further enhance adherence to the prescribed regimen [4]. In the past the efficacy of once-daily administration was, therefore, tested with a number of inhaled steroids in patients with mild-to-moderate asthma [5].

Ciclesonide is a novel prodrug glucocorticosteroid in development for the treatment of asthma. Ciclesonide which has a chiral centre in the acetal side chain, exists as two epimers with different receptor affinities and metabolization rates. Only R-ciclesonide was selected for clinical development (referred to as ciclesonide from now on). Ciclesonide itself is inactive and needs to be cleaved by esterases to bind to the glucocorticoid receptor. The efficacy of ciclesonide in humans was demonstrated in two placebo-controlled trials showing a dose-dependent reduction of airway hyperresponsiveness to adenosine-5′-monophosphate [6] and a significant inhibition of early and late phase reaction after allergen challenge [7].

Ciclesonide is currently developed for once-daily dosing in patients with mild-to-moderate asthma. In the majority of clinical trials carried out so far it was administered as a single dose in the morning and a daily dose of 200 µg was shown to be superior to placebo. In order to tailor asthma management of individuals, a flexible dosing time would be ideal.

The present study, therefore, addressed the question whether the time point of administration (either morning or evening) affects the efficacy of ciclesonide. Based on the results for budesonide [8] the hypothesis was put forward that morning and evening dosing of ciclesonide are equi-effective.

Patients and methods

Patients

Outpatients of either sex, aged 18–75 yrs, with a history of bronchial asthma as defined by American Thoracic Society (ATS) criteria [9] were included.

Patients were eligible to enter the baseline period if they had used rescue medication only during the past 4 weeks and their forced expiratory volume in one second (FEV_1) ranged 50–90% predicted. Patients being pretreated with inhaled steroids (daily doses of up to 500 μg beclomethasone dipropionate (BDP) or flunisolide, 400 μg budesonide and 250 μg fluticasone propionate for at least 4 weeks) were also eligible if their FEV_1 was 80–100% pred. The inhaled steroids were withdrawn at the start of the baseline period. For randomization, FEV_1 had to be 50–90% pred in all patients. In addition, the patients had to show reversibility ($\Delta FEV_1 \geq 15\%$ initial) after inhalation of 200–400 μg salbutamol either during the baseline period or the past 3 months.

Patients were excluded if they had either an asthma exacerbation, an infection of the lower airways, a hospital admission for asthma or if they used systemic steroids in the 4 weeks prior to start of baseline. Patients were also excluded if they suffered from chronic obstructive pulmonary disease (COPD) and/or other relevant lung diseases, or were heavy (ex-) smokers with ≥ 10 pack-yrs. Pregnant, lactating and premenopausal females without safe contraception were ineligible.

Written informed consent was obtained from each patient prior to entering the trial. The protocol was approved by the Ethics Committees of the individual investigators.

Study protocol

The study had a double-blind, randomized, parallel group design. Following a baseline period of 1–4 weeks, the patients were randomly allocated to one of two treatment groups: either ciclesonide in the morning (treatment group "morning") or ciclesonide in the evening (treatment group "evening"). Each patient inhaled one puff of 200 μg ciclesonide at the time point indicated on the label of the inhaler and one puff of placebo at the alternate time point for 8 weeks. Ciclesonide was administered by metered-dose inhaler (MDI) using 1, 1, 1, 2-hydrofluoralkane (HFA) 134a as propellant.

The patients visited the investigational sites at weekly intervals during the baseline period and at 4-weekly intervals during the treatment period or whenever their asthma deteriorated. At each visit lung function was measured and adverse events were elicited by open questioning. At the start of the baseline period, as well as at the end of the treatment period (or upon patient withdrawal), a physical examination including 12-lead electrocardiography (ECG) and a standard safety laboratory work-up was performed. In order to assess the effect of ciclesonide on hypothalamic-pituitary-adrenal (HPA) axis patients collected their 24-h urine at home after 1 week of baseline, as well as at the end of the treatment period and cortisol excretion was determined. Creatinine was also measured in urine to allow for correction in case random or limited time collections were made. The cortisol radioimmunoassay used did not interfere with ciclesonide or its active metabolite.

In an individual subject, all lung function readings (FEV_1, forced vital capacity (FVC)) had to be performed within ± 1.5 h referenced to the randomization visit. The rescue medication had to be withheld for ≥ 4 h prior to each measurement. The highest value from at least three technically satisfactory attempts was used for analysis. Predicted values were calculated according to the formula of the European Coal and Steel Community [10].

No other asthma drugs except rescue medication and trial medication were allowed throughout the trial. Short-acting β-agonists (administered by MDI or powder inhaler) were used to relieve symptoms and the same rescue medication (drug and device) was to be utilized throughout the trial. Cromones (as nasal spray or eyedrops) and histamine 1 receptor (H1)-blockers were allowed to treat symptoms of allergic rhinitis. Nasal and dermatological steroids were not permitted during the 4 weeks before the start of the baseline period as well as during the study. In case treatment with oral steroids became necessary because of an asthma exacerbation, the patient had to be withdrawn from the trial. Those cases were handled as "lack of efficacy" and included in the per-protocol end-point analysis.

Throughout the trial the patients recorded peak expiratory flow (PEF) (Roland® Pulmo-Test AS, Roland Arzneimittel, Hamburg, Germany) daily in the morning, immediately after getting up, and in the evening between 16:00–20:00 h. At the same time symptoms as noted during the night and day, respectively, were recorded applying a four-point scale (*i.e.* the maximum daily score was 8). Additionally, the daily use of the rescue medication had to be documented in a diary. For the diary variables, the mean of all entries made during the week prior to a visit was used for analysis. For the sake of brevity, the average of a weeks measurements of morning PEF are referred to as "morning PEF". The same holds true for accounts of all other diary card variables. Both the investigator and the patient assessed the effectiveness of the trial medication according to a four-point scale: very effective (good control of asthma), effective (not optimal, but acceptable asthma control), slightly effective (moderate asthma control, improvement desired), ineffective (poor control of asthma).

Statistical analysis

Primary efficacy variable was the weekly average of morning PEF (average of last week of study *versus* average of last week of baseline). A sample size of 86 patients per group gives 90% power to correctly conclude equivalence in morning PEF in case of no treatment difference, $\alpha = 0.05$, two-sided, equivalence range of ± 25 $L \cdot min^{-1}$ for the difference in pre/post changes, for which an SD of 50 $L \cdot min^{-1}$ was assumed [11]. Within and between treatment comparisons were based on the differences between end and start of treatment. For lung function variables, equivalence of morning *versus* evening administration was assessed by analysis of covariance with baseline value and age as covariables, and sex and centre as factors.

Table 1. – Patient characteristics

Variable	Itt analysis		pp analysis	
	Morning	Evening	Morning	Evening
Patients n	110	99	88	80
M:F	65:45	49:50	54:34	40:40
Age yrs*	39 (19–75)	38 (18–68)	39 (19–75)	36 (18–68)
Nonsmokers:(Ex-)Smokers	61:49	54:45	49:39	43:37
Pretreated:nonpretreated with ICS	41:69	37:62	31:57	28:52
ICS pretreatment dose in BDP equivalents μg*	500 (50–1000)	500 (200–500)	500 (200–500)	500 (200–500)
FEV_1 % predicted	77±9	77±11	77±9	75±11
Reversibility % baseline	23.5±11	22.8±11	24.5±11	23.8±12
Morning PEF % predicted	90±18	87±20	90±20	86±8

*: Data are presented as median (range). Pretreatment was calculated as 500 μg beclomethasone dipropionate (BDP) = 500 μg flunisolide = 400 μg budesonide = 250 μg fluticasone propionate, irrespective of type of device; Itt: intention-to-treat; pp: per-protocol; ICS: inhaled corticosteroids; FEV_1: forced expiratory volume in one second; PEF: peak expiratory flow.

Equivalence acceptance limits for FEV_1 and FVC changes were chosen as 200 mL. In this equivalence trial, the per-protocol analysis was considered as primary analysis and the intention-to-treat analysis as a secondary one [12]. Treatment differences in the number of drop-outs due to lack of efficacy were analysed by Fisher's exact test. Changes in symptom scores and use of rescue medication were analysed nonparametrically (Wilcoxon-Pratt signed rank test within groups, Mann-Whitney U-Test between groups). Generally, two-sided 95% confidence limits were given for treatment differences. Data are presented as mean±SD unless stated otherwise.

Results

Out of 270 patients enrolled into the baseline period, 209 were randomized. The protocol was violated by 41 patients and these were excluded from the per-protocol analysis which finally comprised 88 patients in the morning group and 80 patients in the evening group (tables 1 and 2 for baseline characteristics). As the study aimed for equivalence, the efficacy results for the per-protocol population are being reported; the results from the intention-to-treat analysis are, however, well in agreement with the per-protocol analysis. With regard to safety, the results refer to all patients randomized who received at least one dose of the trial medication.

Table 2. – Baseline effectiveness variables for patients in the per-protocol analysis

Variable	Morning	Evening
FEV_1 L	2.72±0.67	2.61±0.71
FVC L	3.84±1.01	3.78±1.15
Morning PEF $L \cdot min^{-1}$	446±131	424±117
Evening PEF $L \cdot min^{-1}$	465±123	440±122
Total daily symptom score*	1.57 (0–5.26)	1.57 (0–7.0)
Daily use rescue medication, puffs $24\ h^{-1}$*	1.29 (0–9.0)	1.76 (0–16.83)

*: Data are presented as median (range). For the diary parameters (morning and evening peak expiratory flow (PEF) symptoms, use of rescue medication) the average over the last 7 days prior to start of treatment is being reported. FEV_1: forced expiratory volume in one second; FVC: forced vital capacity.

Morning and evening peak expiratory flow

Compared to the last week of baseline, morning PEF (fig. 1) in the morning group increased by 8 and 3 $L \cdot min^{-1}$ after 4 and 8 weeks of treatment, respectively, which was not significant. In the evening group the improvements at the corresponding time points amounted to 24 and 30 $L \cdot min^{-1}$ ($p < 0.005$) (table 3). The difference between treatments at 8 weeks was significant ($p < 0.05$).

The change in evening PEF after 8 weeks of treatment was 7 $L \cdot min^{-1}$ in the morning group (NS *versus* baseline) and 16 $L \cdot min^{-1}$ ($p < 0.05$) in the evening group (table 3), resulting in a nonsignificant mean difference between treatments of 10 $L \cdot min^{-1}$.

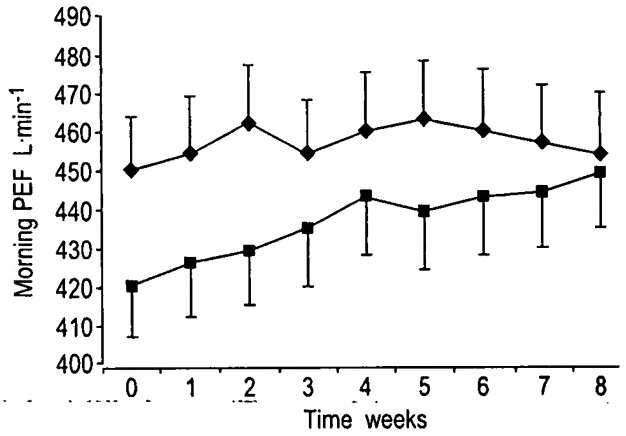

Fig. 1. – Time course mean morning peak expiratory flow (PEF); mean values and SEM. Time point "0" refers to the values recorded during the last week of the baseline period. ◆: morning; ■: evening.

Table 3. – Change in efficacy variables (end *versus* start of 8 weeks treatment)

Variable	Morning	Evening	Morning – evening:
FFEV1 L	0.31 (0.20–0.43)	0.31 (0.19–0.43)	0.00 (-0.15–0.15)
FVC L	0.19 (0.06–0.33)	0.22 (0.08–0.36)	-0.02 (-0.19–0.14)
Morning PEF $L \cdot min^{-1}$	3 (-14–20)	30 (13–48)	-27 (-50–-5)
Evening PEF $L \cdot min^{-1}$	7 (-10–23)	16 (0.4–32)	-10 (-31–11)
Total daily symptom score	-0.38 (-0.80–-0.24)	-0.50 (-0.87–-0.29)	0.02 (-0.29–0.43)
Daily use rescue medication, puffs·24 h^{-1}	-0.36 (-1.00–-0.29)	-0.36 (-1.05–-0.21)	0 (-0.43–0.43)

Lung function: least-squares means and 95% confidence intervals (CI); symptoms and rescue medication: within groups; median and 95% CI, between groups: distribution-free point estimate and 95%-CI. FEV1: Forced expiratory volume in one second; FVC: forced vital capacity; PEF: peak expiratory flow.

Spirometry

Compared to the last baseline reading, FEV1 and FVC increased significantly (at least $p<0.05$) after 8 weeks of treatment in both treatment groups (table 3) and morning and evening administration proved to be equally effective. A similar improvement was observed after 4 weeks of treatment with increases amounting to 200 and 300 mL in the morning and evening for FEV1 and 150 and 250 mL for FVC, respectively. The time course of effect separated for patients either pretreated with inhaled steroids or not, is shown in figure 2.

Symptoms

After both morning and evening administration of ciclesonide, total daily asthma symptoms improved significantly (at least $p<0.001$) after 4 (data not shown) and 8 weeks of treatment (table 3). While during baseline only 21% and 24% of patients in the morning and evening group, respectively, were symptom-free, the percentage of patients without symptoms more than doubled (53% and 55%) after 8 weeks of treatment. No significant difference was found between groups for the total daily score as well as for symptoms reported during the day and night, respectively.

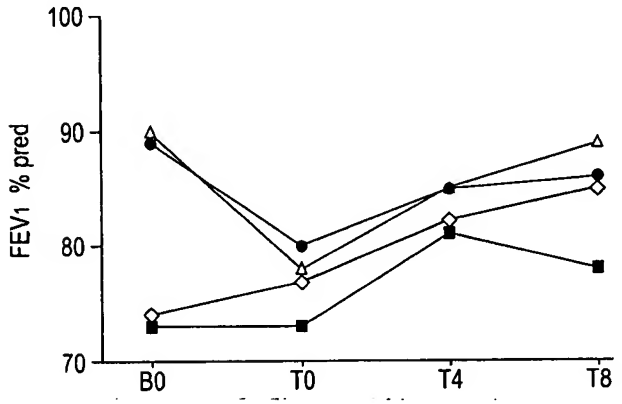

Fig. 2. – Time course in forced expiratory volume in one second (FEV1) in patients either with or without pretreatment with inhaled corticosteroids prior to the study. B0: start of baseline period; T0: time of randomization; T4/T8: after 4/8 weeks of treatment. ◇: morning, not pretreated; ■: evening, not pretreated; ●: morning pretreated; △: evening pretreated.

Use of rescue medication

In both groups the use of rescue medication was significantly (at least $p<0.05$) reduced after 4 (data not shown) and 8 weeks of treatment (table 3). The improvement was comparable in both groups and no significant difference between the groups was found. The same holds true for the percentage of rescue medication free days although this was slightly higher in the morning group (54% *versus* 46% in the evening group).

Lack of efficacy

Lack of efficacy was described in the study protocol as asthma exacerbations to be treated with oral steroids. Eight out of 209 randomized patients (3.8%) in total (four in each group) experienced lack of efficacy.

Efficacy rating

Both the investigators and patients rated ciclesonide as being "very effective" or "effective" in 61% and 63%, respectively, of the patients treated in the morning, and in 71% and 63% with regard to the evening administration.

Safety

Overall, both treatment regimens were safe and well tolerated and there were no differences in the safety aspects between the groups. Eleven patients prematurely left the study because of adverse events; seven in the morning group and four in the evening group. This includes six patients who experienced lack of efficacy as described earlier. The other events leading to withdrawal were one case each of bronchial hypersecretion, nausea/vomiting, dyspnoea and panic attacks, the latter occurring under placebo.

The most frequent adverse events ($\geq 3\%$) concerned the respiratory system (upper respiratory infection: 6.7%; asthma: 6.2%; bronchitis: 4.3%). Two patients (1%) reported voice alterations; no case of candidiasis was described.

Mean 24-h urinary cortisol excretion normalized for creatinine amounted to 8.49 and 8.10 nmol·mmol

creatinine^{-1} (morning and evening group, respectively) during baseline. At the end of treatment, the respective values were 10.47 and 13.88 nmol·mmol creatinine^{-1}. Mean differences within treatment groups (morning: 1.98 nmol·mmol creatinine^{-1} (95% confidence interval (CI): -2.34–6.33); evening: 5.78 nmol·mmol creatinine^{-1} (95% CI: -6.51–18.06)) were not significant as were the differences between treatment groups (-3.80 nmol·mmol creatinine^{-1} (95% CI: -16.79–9.19)). Values below the normal range occurred in 23 patients at baseline and in 15 at the end of the treatment in the morning group, and in 28 and 24 patients, respectively, in the evening group.

Discussion

Results of the present study suggest that 200 μg ciclesonide given once daily is effective in the treatment of mild-to-moderate asthma as assessed by lung function, symptoms, use of rescue medication and number of asthma exacerbations. Although the trial did not have a placebo or active control group, the consistent improvements above baseline values were not only statistically significant but also clinically relevant, and thus support this conclusion.

Morning and evening administration was shown to be equally effective for the different variables, except for morning PEF where the improvements after evening dosing were more prominent. When looking at individual patient responses (see 95% CI in table 3) obviously some patients deteriorated while others improved resulting in no relevant change overall. Hence, the response pattern to a dose given in the morning seems to be more heterogeneous compared to evening administration where all patients had higher values at the end of treatment referred to baseline. It should be noted that baseline morning PEF values in the morning group were higher than in the evening group. It, therefore, might be suspected that a ceiling effect occurred and that the morning group had in fact no room for further improvement. This speculation is, however, not supported by the covariance analysis, which took the differences in baseline into account and nevertheless suggested a significant difference in outcome for the two groups. As two other trials with ciclesonide showed that 100 and 200 μg·day^{-1} given in the morning significantly improved morning PEF compared to placebo, no explanation is, therefore, readily available why this variable was unchanged in the morning group of the current study.

When selecting the optimal time point of administration for an individual patient, the following aspects may be relevant: patient compliance, the fact that asthma can have an important nocturnal component and safety considerations. With regard to compliance, morning dosing of inhaled steroids is favoured [13]. Concerning safety, pharmacokinetic/pharmacodynamic modelling suggests that inhalation of steroids in the afternoon might cause the least cortisol suppression, with the optimum time point being determined by the terminal elimination half-life of the respective drug: *i.e.* an administration time point of 15:00 h was proposed for fluticasone propionate and of 19:00 h for flunisolide [14]. Finally, due to the circadian rhythm in lung function, hyperresponsiveness, circulating cells and mediators in asthma, it might be expected that based on the results with oral and intravenous steroids [15, 16], afternoon/evening dosing of inhaled steroids is preferable to morning dosing for alleviation of nocturnal worsening in asthma.

Morning administration of budesonide was shown to be superior to placebo [17] and the authors concluded that recommendation for the time of dosing may well be left to the individual physician. Several studies evaluated the efficacy of evening dosing of budesonide and with the exception of one trial [4] they all found that evening administration is at least as effective as twice-daily dosing [18–20]. In addition, JONES *et al.* [8] addressed the issue of time of dosing and concluded that morning and evening administration of budesonide are equi-effective. Similar findings were made for flunisolide; although for morning PEF and daytime use of rescue medication there was a trend in favour of evening dosing [21]. The efficacy of 100 μg fluticasone propionate twice-daily was generally greater than a 200 μg once-daily morning regimen in patients pretreated with inhaled steroids, whereas no such difference was seen in patients pretreated with bronchodilators only [22]. Hence, there is clear evidence from the literature that once-daily dosing of inhaled steroids is an effective regimen for the treatment of mild-to-moderate asthma. No final conclusion is yet possible about the ideal time point of administration although some studies suggest that morning dosing might be less efficacious. In fact PINCUS and coworkers [13, 23] proposed that administration of inhaled steroids in the afternoon between 15:00–17:30 h might result in the most pronounced asthma control. However, afternoon administration does not necessarily increase compliance and as the present trial suggests, relevant improvement can also be achieved by evening dosing between 16:00–20:00 h, the time window for optimal administration of inhaled steroids might in fact be wider. This is also in line with a study investigating the efficacy of a single dose of 1,000 μg BDP·day^{-1} in the late afternoon (17:00 h) and at bedtime (22:00 h) showing comparable asthma control for both regimens [24].

The safety data of the current trial suggest that ciclesonide was well tolerated. No influence on HPA axis was found as judged by 24-h urinary cortisol suppression. This is in line with the results of a study in healthy volunteers where the 24-h mesor for serum cortisol under ciclesonide (800 μg), given either in the morning or in the evening for one week, was 2–6% lower compared to placebo indicating that ciclesonide lacks relevant systemic effects [25]. Hence, from a safety point of view ciclesonide can be administered both in the morning or evening.

Although the question on the ideal time point of once-daily administration of inhaled steroids warrants further investigation, the current study suggests that ciclesonide can be given either in the morning or in the evening so that patient preference and individual medical needs can be addressed.

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Exhibit C

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Feasibility and response to budesonide as topical corticosteroid therapy for acute intestinal GVHD

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Summary:

Therapy of acute intestinal GVHD is still one of the main challenges after allogeneic transplantation. Increasing systemic immunosuppression (IS) is the first choice and includes corticosteroids and lymphocyte antibodies, often associated with severe side-effects. In inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, topical steroid therapy is used very successfully. Because of the similarity between these and acute intestinal GVHD we conducted a trial with oral budesonide (Budenofalk), a new topically active glucocorticoid, to treat patients with acute GVHD ≥ grade II. After a diagnosis of aGVHD ≥ grade II, 22 patients received increased IS, mainly systemic corticosteroids, and additionally budesonide 9 mg/day divided into three doses. Improvement in aGVHD, infectious side-effects, reduction of systemic IS and outcome were documented. Results were compared with the results of 19 control patients, who were treated only by increasing IS dose. In 17/22 patients (70%), treated with budesonide, the acute intestinal GVHD resolved and no relapse occurred after decreasing the systemic IS, while continuing budesonide. In only 8/19 patients in the control group did the acute intestinal GVHD resolve and 2/8 patients had a relapse of intestinal GVHD after decreasing IS, with an overall response of 33%. No severe intestinal infections occurred. We conclude that budesonide may be effective in acute intestinal GVHD as a topical corticosteroid and prospective, randomized studies should demonstrate its efficacy in allowing reduction of systemic immunosuppressive therapy, and its side-effects.

Keywords: acute intestinal GVHD; budesonide; endoscopy; topical corticoid therapy

Successful treatment of hematological malignancies by allogeneic transplantation is commonly limited by relapse of the malignancy, by infection or by GVHD. The gastrointestinal tract is one of the prominent target organs involved in acute GVHD after allogeneic transplantation and morbidity to it is an important cause of death. Therapy includes intensification of immunosuppressive therapy (eg cyclosporin A (CsA), monoclonal antibodies, increased doses of systemic glucocorticoids, ATG).[1] Systemic corticosteroid therapy may lead to severe side-effects such as myopathy, osteoporosis, cataract and increased susceptibility to infections. With beclomethasone dipropionate, a topical corticosteroid administered orally, promising results have been reported in the treatment of acute intestinal GVHD.[2,3] Budesonide (BUD) is a new topical active glucocorticoid with a high affinity for the glucocorticoid receptor[4] and high anti-inflammatory activity. Budenofalk capsules (Dr Falk Pharma GmbH, Freiburg, Germany) are a preparation releasing budesonide at pH ≥ 6.4 which is mainly resorbed in the terminal ileum and ascending colon.[5] Half-life of this preparation is 3.0 h.[6] The systemic bioavailability of BUD is extremely low[7] due to rapid first pass metabolism in the liver.[8] Budesonide is already used very safely and successfully in bronchial asthma and allergic rhinitis[9] and in chronic inflammatory bowel diseases (ulcerative colitis[10] and Crohn's disease[4,5]). It has been shown that the side-effects in the BUD treatment group in Crohn's disease were comparable to a placebo group.[11] In patients with ulcerative colitis it was also demonstrated that treatment with BUD is safe, and as effective as treatment with prednisolone. Interestingly, the typical corticoid side-effects are dramatically diminished and the plasma corticoid level remained normal in the BUD treatment group in contrast to the systemic prednisolone treatment group.[12] Additional studies showed that treatment with a daily dose of 9 mg BUD does not disturb pituitary–adrenal function.[13–15] Because of the promising results in the treatment of inflammatory bowel disease, all patients from December 1994 to April 1997 with acute GVHD of the gastrointestinal tract ≥ grade II were offered treatment with oral budesonide in addition to standard increases in systemic immunosuppression. Reduced treatment efficiency was unlikely as budesonide was given in addition to standard increases in systematic immunosuppression after a diagnosis of acute intestinal GVHD. The aims of this study were to avoid and/or reduce corticoid side-effects by rapid tapering of the systemic corticosteroid dose and to reach a faster resolution of aGVHD. Here, we show the feasibility of budesonide therapy and the response to this drug in 22 patients with acute intestinal GVHD. Clinical grading, macroscopic staging of endoscopically visible lesions and histological grading were used as parameters. Data of efficacy from all adult patients since 1990 until April 1997, who suffered from acute intestinal GVHD ≥ II and did not

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receive BUD were reviewed as a control group in respect of clinical characteristics and outcome. These patients did not receive BUD because they were treated before BUD was available ($n = 13$) or because they refused to participate ($n = 6$).

Patients and methods

Between July 1990 and April 1997, 274 patients underwent allogenic bone marrow or peripheral stem cell transplantation at the University Medical Center and Children's Hospital of the Albert Ludwig University Freiburg. During this period 41 patients were diagnosed with acute intestinal GVHD > grade I (15%) (Table 1). Since December 1994 BUD has been available and all of these patients were asked to participate in a trial with addition of BUD. Nineteen adults and three children (nine females/13 males) agreed and received budesonide for intestinal GVHD. The median age was 31 years (range 6–53). Underlying diseases were CML $n = 4$, AML $n = 6$, ALL $n = 6$, multiple myeloma (MM) $n = 2$, JMML $n = 1$ and MDS $n = 3$. In 10 patients a sibling, in 11 patients a MUD and in one patient a haploidentical relative served as the donor. Conditioning therapy consisted of BU/CY/MEL ($n = 1$), BU/CY ($n = 15$), TBI/CY ($n = 3$), TBI/VP16/CY ($n = 3$). Nine patients received CsA/MP/MTX, $n = 6$ CsA/MP, $n = 1$ CsA/MTX, $n = 3$ CsA/MP/ATG and $n = 2$ only CsA for GVHD prophylaxis (Table 1).

Table 1 Patients' characteristics

	Study group $n = 22$	*Control group* $n = 19$
Study period	1994–1997	1990–1997
		1990 $n = 1$
		1991 $n = 3$
		1992 $n = 2$
		1993 $n = 3$
	1994 $n = 4$	1994 $n = 4$
	1995 $n = 12$	
	1996 $n = 4$	1996 $n = 4$
	1997 $n = 2$	1997 $n = 2$
F/M	9/13	7/12
Age (years)	31	38
Median range	(6–53)	(21–54)
Donor		
MUD	11	11
Sib	10	8
MmSib	1	
Diagnosis		
CML	4	6
AML	6	4
ALL	6	2
MM	2	1
JMML	1	
MDS	3	3
SAA		3
Onset of aGVHD		
Day + (range)	30.5 (10–310)	38 (15–73)
Other sites involved	11 (50%)	13 (70%) NS

NS = not significant.

Nineteen adult patients (seven female; 12 male) with a median age of 40 years (range 21–54) who were treated for acute intestinal GVHD ≥grade II without budesonide because they denied participation ($n = 6$) or were treated before December 1994 ($n = 13$), served as a control group. In 11 patients a MUD and in eight patients a sibling served as graft donor (CML $n = 6$, AML $n = 4$, SAA $n = 3$, ALL $n = 2$, MM $n = 1$, MDS $n = 3$).

All transplants were performed as standard procedures as published before.[16] Routinely on day +30 and +100, or in the case of diarrhea, a sigmoidoscopy was performed for macroscopic and histologic evaluation of the colon. In cases of vomiting, nausea and stomach pain a gastroscopy was performed. Clinical grading of GVHD was defined according to Glucksberg.[17] Histological classification of the biopsies for aGVHD was done according to Snover[18] and Lerner *et al*[19] and macroscopic grading was done according to Kreisel.[20] None of the patients had culture or histologically proven intestinal bacterial, fungal or viral infections. After diagnosis of acute GVHD ≥ II in one of the above mentioned gradings immunosuppressive therapy was intensified mainly by increasing the systemic corticosteroid dose to a total dose of 2 × 1 mg/kg bw, and by increasing CsA to reach an estimated blood level of 250 ng/ml whole blood. For prophylaxis of infectious complications patients received metronidazole 800 mg/day, ciprofloxacin 500 mg/day and amphothericin B 0.5 mg/kg bw/day. Since 1994 pre-emptive CMV therapy has been initiated in the event of two positive PCR samples on two occasions, but even before 1994 no patient suffered from CMV colitis. Additionally, patients in the study group received budesonide (Budenofalk) after informed consent, at a daily dose of 9 mg divided into three doses in order to obtain constant corticoid levels in the gut. Diarrhea volume and frequency as well as abdominal pain were registered. Stool analysis was performed regularly for micro-biological pathogens. A control endoscopy was done, if clinical symptoms did not resolve. If the symptoms improved the systemic corticoid dose was rapidly tapered, but the dosage of budesonide was still maintained. Resolution of GVHD was documented. Decrease of stool volume and frequency of bowel movements were taken as markers for the resolution of intestinal GVHD. Potential side-effects of budesonide such as vomiting, nausea were documented. Special attention was paid to possible occurrence of a new intestinal infection by weekly, regularly stool surveillance cultures.

Results

Clinical, endoscopic and histological results (Table 2)

Intestinal GVHD was observed at a median of 30.5 days (range 10–310) after transplantation in the study group and at a median of 35 days (range 15–75) in the control group. In 21/22 patients in the BUD group a sigmoidoscopy was performed and GVHD grade I/II was diagnosed in $n = 9$ (39%), grade III in $n = 8$ (34%) grade IV in $n = 2$ (9%) cases. In 1/21 patients macroscopic appearances were

Table 2 GVHD grading

	Study group	*Control group*
Endoscopic findings (UGI and LGI)	*n = 20[a] (%)*	*n = 19 (%)*
Grade		
I/II	10 (50)	9 (48)
III	8 (40)	6 (31)
IV	2 (10)	4 (21)
Histology grading (UGI and LGI)	*n = 14[b] (%)*	*n = 19 (%)*
same as endoscopic	8 (57)	17 (89)
1 grade difference	4 (29)	2 (11)
2 grade difference	2 (14)	
Clinical grading (LGI)	*n = 21 (%)*	*n = 17[b] (%)*
same as endoscopic	11 (55)	11 (65)
1 grade difference	10 (45)	5 (29)
2 grade difference		1 (6)

UGI = upper gastrointestinal tract; LGI = lower gastrointestinal tract.
[a]Not all children received endoscopy.
[b]Complete data could not be obtained in all patients.

defined as normal and in one patient as colitis. In four patients an additional gastroscopy was performed revealing grade I and II in three cases, and grade IV in one case. In UPN 960243 gastroscopy only was carried out which was macroscopically grade II. Macroscopic and histological grading of intestinal GVHD were reviewable in 14 cases. In 8/14 (57%) the same grade was seen, in 4/14 (29%) it differed by one, and in 2/14 (14%) by two grades. The clinical course of the GVHD was graded by experienced practitioners. For the lower GI tract, grade I/II was diagnosed in 10/21 (47%), grade III in 5/21 (24%) and grade IV in 6/21 (29%) cases. Corresponding macroscopic results were identical in 11/21 cases (55%) and differed only by one grade in all other cases (45%), mainly in patients with grade III or IV.

For patients in the control group, endoscopic examination of the gut showed aGVHD grade II in nine cases (47%), grade III in six patients (32%) and grade IV in four patients (21%). In 17/19 patients (89%) endoscopic grading was identical with the histological examination, in 13/19 endoscopy showed the same result as the clinical grading and in 11/19 clinical and histological situations were identical.

Apart from the GVHD of the GI tract, 11/22 patients (50%) in the study and 13/19 patients (70%) in the control group had additional manifestations of GVHD at other sites, mainly liver and skin.

Immunosuppression at start of BUD therapy

At the start of BUD therapy 19/22 patients were still receiving systemic MP and CsA and the MP dose was increased mostly by doubling the dose. UPN 960215 was off MP, which was reintroduced with 1 mg/kg bw. UPN 950180, who received only CsA for GVHD prophylaxis, was treated only with BUD without MP, having clinical and histologically proven aGVHD grade III.

Duration of BUD therapy and side-effects

Twenty patients received BUD for a median period of 24 days (range 6–70). Two patients (10%) were enrolled in the study but no final results could be obtained, because on day 7 or 8 respectively, they could no longer swallow the capsules and received only i.v. immunosuppression (MP and CsA). Side-effects were not observed in any patient, in particular, no severe infections of the bowel. After initiating oral BUD, *Torulopsis glabrata* was found in the stool of only one patient (UPN 950159) as a new intestinal pathogen.

Resolution of GVHD in the study group (Table 3)

Clinical improvement of the intestinal GVHD was defined as decrease of stool frequency and volume. In five cases it was verified by macroscopic re-evaluation of the colon. As soon as improvement in intestinal GVHD was documented, the dose of MP was reduced to 50% of the maximum dose. In 17/22 patients (77%) (nine patients with grade II, five patients with grade III and three patients with grade IV) intestinal GVHD resolved and no relapse occurred. Both patients who could not continue the budesonide, because of deterioration in performance status, and three patients, who did not improve during BUD therapy, died due to acute GVHD with multi-organ failure. All five had grade III (two patients) or grade IV (three patients) intestinal GVHD and involvement of other organs. Four had a MUD/mismatched related and one had a matched related donor. Improvement was seen at a median of 12 days (range 3–28) after increasing the MP dose and starting the BUD therapy. The median systemic methylprednisolone dose until improvement or death was 3.8 g (range 1–12 g) and the median budesonide dose was 193 mg (54–725 mg).

Immunosuppression during and at the end of BUD

In 17 patients with improvement of GVHD it was possible to decrease the MP dose at a median of 12 days (6–25). Therapy with BUD was continued in all cases until the dose of MP was reached, which was given to patients before the

Table 3 Therapy and outcome

	Study group n = 22	*Control group n = 19*	
Methylprednisolone increased	20 (90%)	19 (100%)	
Budesonide therapy	22 (100%)	—	
Resolution of aGVHD	17 (77%)	8 (42%)	
Relapse	0	2 (10%)	
Overall response	17 (77%)	6 (32%)	$P < 0.01$ (significant)
Median day until improvement	12 (3–28)	13 (7–18)	NS

NS = not significant.

onset of GVHD. Thereafter, BUD was discontinued in 8/17 (47%) cases and tapered in 9/17. No relapse of intestinal GVHD occurred after decreasing the MP dose while patients were still on BUD and after cessation of BUD.

Resolution of GVIID in the control group (Table 3)

After intensification of systemic immunosuppressive therapy, intestinal GVHD resolved in 8/19 patients (42%) but showed no improvement in 11/19 patients (58%). In 2/8 the acute intestinal GVHD relapsed after tapering the corticosteroid dose. Overall, 13/19 patients (68%) died due to aGVHD. The median dose of systemic methylprednisolone until improvement in intestinal GVHD or death in this group of patients was 4.5 g (1–15 g) and the time prior to improvement in the six patients (32%), who survived, was 13 days median (range 7–18).

Discussion

Systemic corticosteroids are the most effective immunosuppressive agents for treatment of aGVHD. The disadvantages are the many side-effects. Through the therapy of Crohn's disease and ulcerative colitis we have learned that inflammatory reactions of the gastrointestinal endothelium induced by immunological processes respond well to topical glucocorticoids (beclomethasone, budesonide, fluticasone).[4,5,21] Both acute intestinal GVHD and Crohn's disease seem to have a similar pathogenic background, in that reactions against intestinal epithelial cells occur. Both diseases present with comparable macroscopic appearances and localization in the gastrointestinal tract. We therefore decided to treat our patients with BUD in addition to standard systemic CsA/MP therapy. The daily dose of 9 mg/day was divided into three doses to keep a constant local corticoid level.[22] In our retrospective survey BUD therapy was feasible and very well tolerated without any enteric infections or local complications, except for one new fungal infection in the stool without clinical significance. In 17/22 patients (77%) receiving BUD the acute intestinal GVHD resolved compared to 42% in the patients without additional BUD (Table 3). These data are similar to the recently published results showing a 71% response to beclomethasone treatment compared to 55% in the control group.[3] In our survey, despite the fast reduction of MP, no relapse occurred while BUD was continued. This was also observed for Crohn's disease in placebo controlled studies, showing that low-dose BUD prolongs time to relapse.[23,24] In our control group, two patients relapsed after decreasing the systemic corticosteroid dose. Overall, in this group only 32% reached a long-term resolution of acute intestinal GVHD without BUD. Although it is a nonrandomized trial these results show a significant difference ($P > 0.01$) in the unpaired t-test. Furthermore, our data confirm the importance of endoscopic grading for diagnosis and grading of acute intestinal GVHD, because of the good correlation of endoscopic, histological and clinical classifications of aGVHD (Table 2).[20]

We conclude that the pH-modified budesonide preparation was very well tolerated in patients with acute intestinal GVHD. Early initiation of the budesonide therapy should be performed to stop destruction of the intestinal mucosa or to allow recovery of the endothelium, thereby avoiding bacteremia or fungemia. Our retrospective analysis may form the basis for a randomized study necessary to prove our results and show whether early extensive reduction of systemic immunosuppression is possible to avoid severe corticoid side-effects. In cases of local GVHD of the recto/sigmoid the application of a budesonide foam should be considered, especially in patients who are unable to swallow.

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Exhibit D

Oral budesonide is as effective as oral prednisolone in active Crohn's disease

M Campieri, A Ferguson, W Doe, T Persson, L-G Nilsson, and the Global Budesonide Study Group

Abstract

***Background*—The use of corticosteroids in active Crohn's disease often becomes limited by side effects. Budesonide is a potent corticosteroid with low systemic bioavailability due to an extensive first pass liver metabolism.**

***Aims*—To compare the efficacy and safety of two dosage regimens of budesonide and prednisolone in patients with active Crohn's disease affecting the ileum and/or the ascending colon.**

***Patients and methods*—One hundred and seventy eight patients were randomised to receive budesonide controlled ileal release (CIR) capsules 9 mg once daily or 4.5 mg twice daily, or prednisolone tablets 40 mg once daily. The treatment period was 12 weeks. The primary efficacy variable was clinical remission, defined as a Crohn's Disease Activity Index (CDAI) of 150 or less.**

***Results*—After eight weeks of treatment, remission occurred in 60% of patients receiving budesonide once daily or prednisolone and in 42% of those receiving budesonide twice daily (p=0.062). The presence of glucocorticoid associated side effects was similar in all groups; however, moon face was more common in the prednisolone group (p=0.0005). The highest frequency of impaired adrenal function, as measured by a short ACTH test, was found in the prednisolone group (p=0.0023).**

***Conclusions*—Budesonide CIR, administered at 9 mg once daily or 4.5 mg twice daily, is comparable to prednisolone in inducing remission in active Crohn's disease. The single dose administration is as promptly effective as prednisolone and represents a simpler and safer therapeutic approach, with a considerable reduction in side effects.**

(*Gut* 1997; 41: 209–214)

Keywords: adrenal function; CDAI; glucocorticoid; glucocorticoid associated side effects

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Crohn's disease is a chronic inflammatory disorder of unknown aetiology. Although any portion of the digestive tract from mouth to anus may be involved, the most commonly affected parts are the distal ileum and the ascending colon.[1] To date, glucocorticoids (GCS)—prednisone or prednisolone—have been the most effective drugs in inducing clinical remission in these patients with Crohn's disease[2]; unfortunately their therapeutic efficacy is counterbalanced by unwanted side effects attributable to their absorption and pharmacological (systemic) action or to their suppression of endogenous adrenal function.[3] Moreover, in clinical practice it has often been difficult to wean patients off systemically active GCS without triggering a relapse of the disease. New GCS have been developed which possess potent topical anti-inflammatory activity and with a systemic activity less than conventional GCS.[4] The unique therapeutic ratio of the new analogues is due to a high potency combined with their extensive and rapid first pass liver metabolism, where the metabolites have minimal or no GCS activity.

Budesonide is the most extensively studied compound of this new group of GCS. When administered by inhalation, budesonide has been found to be effective and safe in the treatment of both asthma and rhinitis.[5] Given as an enema, it has also been found to be as effective as conventional GCS enemas in the treatment of distal ulcerative colitis but has the clear advantage of producing significantly less adrenal suppression than conventional GCS.[6–9]

Budesonide has also been developed in a gastric resistant formulation (Entocort® capsules, Astra Draco, Lund, Sweden) containing pellets with slow release properties; this preparation allows the drug to be delivered mainly to the ileum and ascending colon.[10] The properties of this formulation, together with the high GCS potency and extensive first pass liver metabolism of budesonide, offer improved therapy for Crohn's disease by reducing the risk of steroid associated side effects. In previous studies,[11–13] budesonide controlled intestinal release (CIR) capsules 9 mg daily were effective in inducing remission in patients with active Crohn's disease affecting the ileum and the ascending colon. In a placebo controlled dose finding study,[12] budesonide CIR 4.5 mg twice daily was found to be the lowest effective dose, while in a study designed to compare budesonide 9 mg once daily and prednisolone 40 mg,[13] both agents were equally effective in inducing remission.

However, prednisolone reduced the mean Crohn's Disease Activity Index (CDAI) scores significantly more, whereas budesonide 9 mg once daily gave rise to significantly fewer glucocorticoid associated side effects and less suppression of endogenous cortisol production. It was felt important to study further the clinical efficacy of budesonide and the impact on the adrenal glands in comparison with

prednisolone, and whether there were any differences if budesonide was given once or twice daily.

Methods

SELECTION OF PATIENTS

Twenty six investigational centres in the United Kingdom, Ireland, Italy, Australia, New Zealand, Germany, Sweden, Belgium, and The Netherlands participated in the study.

Eligible patients were older than 18 years of age, with a confirmed diagnosis of active Crohn's disease, as defined by a score of 200 or higher on the CDAI.[14] The extent of disease had to be defined within 24 months before randomisation; entry was restricted to patients with disease involving the ileum and/or the ascending colon but not extending beyond the hepatic flexure. Patients who had undergone ileostomy or more extensive resection of the ileum (>100 cm), and those with severe disease requiring imminent surgery, were not enrolled in the study. They were not eligible if they had complications including abscesses, perforations, or active fistulas. Patients with concomitant active peptic ulcer or clinically important hepatic, renal, cardiovascular, or psychiatric conditions were also excluded. Immunosuppressive drugs were allowed until three months before the study, 5-aminosalicylates and metronidazole until the day before the study, and corticosteroids allowed until one week before the study. The trial was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committees at all centres; all patients gave written or oral informed consent.

STUDY DESIGN

The trial was a randomised double blind, double dummy study. A baseline CDAI was obtained during a run-in period of three to seven days. The patients were subsequently randomised to treatment with either budesonide CIR capsules 9 mg once daily or 4.5 mg twice daily or prednisolone 40 mg once daily. Budesonide CIR was tapered to 6 mg after eight weeks and to 3 mg after a further two weeks. Prednisolone was tapered to 30 mg after two weeks and then continuously throughout the study, reaching 5 mg after nine weeks. The 5 mg dose was then continued for three weeks so that the total treatment period was 12 weeks. Follow up visits were carried out after two, four, eight, and 12 weeks of treatment.

STUDY DRUGS

The controlled ileal release gelatine capsules containing 3 or 1.5 mg budesonide used in the study (Entocort® capsules) and placebo capsules were manufactured by Astra Draco AB (Lund, Sweden). The prednisolone tablets, 5 and 10 mg, and placebo tablets were obtained from As Hydro Pharma (Elverum, Norway). The drugs were provided in identical blister packages. Compliance was checked by the study personnel by counting unopened blisters. Patients were considered non-compliant if they consumed less then 75% of the study drugs during their actual treatment period or if they interrupted the study drugs for more than five consecutive days.

CLINICAL ASSESSMENT

At entry, patients' demographic characteristics, relevant current and past diagnoses, current medication, and history of previous bowel surgery were recorded. The distal part of the colon was assessed by sigmoidoscopy to exclude inflammation in the rectum. Disease extent was confirmed by endoscopy or radiology assessment if not done within the 24 months prior to the first visit.

CDAI was the main clinical assessment for determination of drug efficacy and it was calculated at the randomisation visit and at all subsequent visits. Remission was defined as a CDAI of 150 or less. The patients were provided with diary cards for all weeks of the study. On these, they recorded (each evening) the number of stools, general well being, abdominal pain, and intake of study medication. Adverse events were also recorded at each visit, as responses to a standard question ("Have you had any health problems or symptoms not usually associated with your bowel disorder since the last visit?"). Scores from the seven days preceding the clinic visit were used for the CDAI calculation.

The following analyses were done at each visit and used as measures of inflammation: erythrocyte sedimentation rate (ESR), platelet particle concentration, serum C-reactive protein (CRP) (before treatment and after four and 12 weeks), and serum orosomucoid.

Safety assessments consisted of the recording of any symptoms, clinical and haematological measurements, and an examination by the investigator for corticosteroid associated side effects. Blood samples for plasma cortisol analysis were drawn between 7.30 and 9.30 am, always at the same time on each occasion.

SHORT ACTH TEST

The responses to the short ACTH test (Synacthen®, Ciba-Geigy), at randomisation and after eight weeks of treatment, were analysed with regard to plasma cortisol concentrations before and 30 minutes after the ACTH injection; the magnitude of the increase was determined. Plasma cortisol concentration was analysed both at the centre and at Astra Draco AB. The analyses carried out at each centre were used only for safety purposes, whereas the results from analyses done at Astra Draco AB, using an HPLC method,[15] are reported here. The adrenal function was considered normal if the 0-minute plasma cortisol level was $\geq$150 nmol/l and either the plasma cortisol increase was $\geq$200 nmol/l or the 30-minute plasma cortisol concentration was $\geq$400 nmol/l.

STATISTICAL ANALYSIS

From the National Cooperative Crohn's Disease Study (NCCDS) and other reports it was estimated that the remission rates after 10 weeks would reach 70% in the prednisolone

group.[14 16 17] No or little difference in efficacy between the two budesonide regimens was assumed, while there might possibly be a difference between either of the budesonide regimens and prednisolone. The primary aim of this study was to assess the remission rates after two, eight, and 12 weeks of treatment. With 50 patients per group there was an 80% probability of detecting a significant difference if the budesonide remission rate was 40%. A 95% confidence interval for the difference in remission rates between any two groups would have an uncertainty of ±19%. In order to compensate for non-evaluable patients, it was estimated that 180 randomised patients would be required. The analyses were based on data for all patients treated and the last available value after the baseline value. No correlations for multiple comparisons have been made.

Results

PATIENT ENROLMENT

A total of 178 patients were randomised and 177 were treated; 58 patients received budesonide 9 mg once daily, 61 budesonide 4.5 mg twice daily, and 58 received prednisolone. The demography and disease history for all patients treated, recruited at 26 centres, are presented in table 1. The groups were well matched. Out of the 177 patients treated in the study, 36 prematurely discontinued their treatment.

The major reason (15%) for treatment withdrawal was disease deterioration or no improvement (therapeutic failure). The frequencies of therapeutic failure observed were comparable in the three groups—that is, 16% in the budesonide once daily group,16% in the budesonide twice daily group, and 12% in the prednisolone group. A χ^2 test showed no significant differences between the treatment groups (p=0.78).

CLINICAL EFFICACY

Remission rates

Statistical evaluation of all patients treated showed that after two weeks of treatment the highest remission rate of 48% was observed in the budesonide once daily group, compared with 37% in the prednisolone group, and 27% in the budesonide twice daily group (fig 1). These differences in remission rates were not significant (p=0.052). After eight weeks treatment, equal remission rates of 60% were found in the budesonide once daily and prednisolone groups, compared with 42% in the budesonide twice daily group (fig 1). The differences between the three groups were not statistically significant (p=0.062).

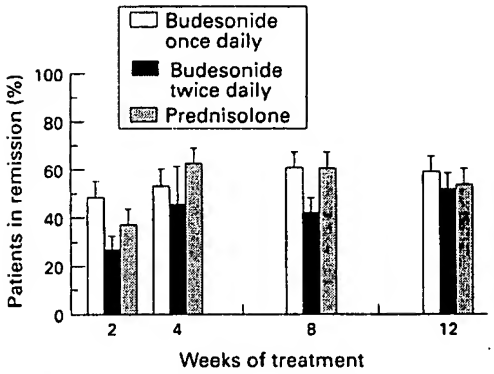

Figure 1: Mean (SE) proportion of patients in remission after two, four, eight, and 12 weeks of treatment with budesonide or prednisolone.

Analyses with respect to prognostic factors

Analyses of remission rates by two-way analysis of variance were also performed with respect to the following prognostic factors:

- disease activity at inclusion (CDAI ≥300/ CDAI <300)
- previous bowel resection (yes/no)
- sex
- previous steroid treatment during the past year (yes/no).

After eight weeks of treatment patients admitted to the study with a CDAI <300 showed an overall remission rate significantly higher than patients who entered with a CDAI >300. Of the patients admitted with a CDAI <300, remission was achieved in 31/44 in the budesonide once daily group, in 21/40 in the budesonide twice daily group, and in 22/44 in the prednisolone group. In the group with a CDAI ≥300, remission was achieved in 4/13, 3/18, and 7/13 in the budesonide once daily, budesonide twice daily, and prednisolone groups, respectively. Disease activity was a prognostic factor which significantly (p=0.0007) influenced the remission rates; however, the difference between treatments did not depend on the disease activity. Furthermore, the absolute decrease in mean CDAI was largest in the budesonide once daily group, irrespective of severity at entry.

There was a statistically significant interaction between treatment and the presence or absence of previous resection (p=0.030); although the remission rate was higher among non-resected patients in both the budesonide once daily group and the prednisolone group, the rate was higher among resected patients in the budesonide twice daily group. Remission rates for male or female patients, or for patients who had or did not have previous steroid treat-

TABLE 1 *Demographic characteristics and disease history*

	Budesonide once daily (n=58)		*Budesonide twice daily (n=61)*		*Prednisolone (n=58)*	
	Mean	*Range*	*Mean*	*Range*	*Mean*	*Range*
Sex ratio (M/F)		21/37		28/33	23/35	
Age (years)	36	17–71	38	20–71	36	19–70
Weight (kg)	63	41–118	63	35–94	61	39–93
CDAI	277	121–476	274	107–465	279	202–458
Disease duration (years)	8.3	0–30	7.9	0–37	6.7	0–27
Current exacerbation (months)	4.0	0–46	7.6	0–98	5.5	0–65
Previous resection (Y/N)		28/30		27/34		34/24
Time since resection (years)	5.8	0–22	5.3	0–23	4.6	0–13

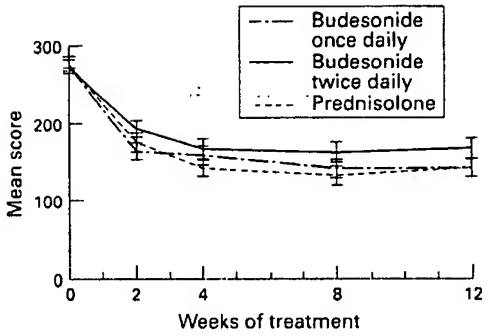

Figure 2: Mean (SE) CDAI score at randomisation and after two, four, eight, and 12 weeks of treatment with budesonide or prednisolone.

ment, were not significantly different (p=0.80, p=0.15).

CDAI change

The mean initial CDAI score was 277 for the budesonide once daily group, 274 for the budesonide twice daily group, and 279 for the prednisolone group. The most pronounced decrease in CDAI score in all three groups was observed during the first two treatment weeks.

As reflected by remission rates, the mean CDAI scores decreased more in the budesonide once daily group and prednisolone group than in the budesonide twice daily group. The difference between the groups in reduction of CDAI score was statistically significant after two weeks (p=0.050) but not after eight weeks (p=0.093) (fig 2).

SAFETY RESULTS

Adverse events

Adverse events (any unfavourable events—such as clinical signs, symptoms, changes in laboratory data—temporarily associated with administration of the study drug) were registered in 78% of patients in the budesonide once daily group, 90% in the budesonide twice daily group, and 90% in the prednisolone group. Most adverse events were related to the gastrointestinal system, probably reflecting the underlying disease. A slightly higher frequency of dyspepsia was observed in the budesonide once daily group, while nausea and epigastric pain were more frequent in the budesonide twice daily group. The highest frequency of patients with Cushingoid features was observed in the prednisolone group. Four patients in the budesonide once daily group reported rashes compared with none in the other groups; the frequency of depression and insomnia, palpitations, and flushing was higher in the prednisolone group. The number of patients with urinary tract infections was higher in the budesonide twice daily group whereas increased frequency of micturition was reported only by prednisolone treated patients.

Eighteen adverse events in 17 patients, of which 10 discontinued study treatment, resulted in hospitalisation and were classified as serious. The majority of admissions were for disease deterioration or complications of Crohn's disease. A relationship between these serious adverse events and the study drug was judged, by the investigator, to be unlikely.

There was a significant difference between the three groups with respect to change in weight: after eight weeks, mean body weight increased by 1.0 kg in the budesonide once daily group and by 2.1 kg in the prednisolone group, but not at all in the budesonide twice daily group (p<0.0001).

Haematology, clinical chemistry, and inflammatory indicators

Most of the laboratory values found outside normal reference ranges were considered by the investigators to be related to the underlying Crohn's disease. There were no statistically significant differences between the three groups with respect to changes in the inflammatory indicators (ESR, serum CRP, serum orosomucoid).

Comparison of the mean changes in haematological and clinical chemistry variables from baseline showed a significant difference (p=0.029) at 12 weeks between the groups with respect to leucocyte count. After 12 weeks the mean leucocyte count in the prednisolone group significantly increased by 0.9×10^9/l; it decreased by 0.5×10^9/l in the budesonide once daily group, and very slightly increased by 0.1×10^9/l in the budesonide twice daily group. No other haematological and clinical chemistry variables differed significantly between the groups.

Basal plasma cortisol

The mean plasma cortisol values at randomisation were similar in the groups—that is, 382 nmol/l in the budesonide once daily group, 374 nmol/l in the budesonide twice daily group, and 375 nmol/l in the prednisolone group. There was a decrease in all three groups during the treatment period (fig 3). After eight weeks of treatment the mean plasma cortisol value had decreased by 258 nmol/l in the prednisolone group, by 194 nmol/l in the budesonide once daily group, and by 132 nmol/l in the budesonide twice daily group. The difference between the groups was statistically significant (p=0.0035). There was no significant difference between the two budesonide groups (p=0.096). Mean plasma cortisol values after two, eight, and 12 weeks were always lower in the prednisolone group.

The proportion of patients with values below the lower plasma cortisol normal reference limit—150 nmol/l—was significantly higher in

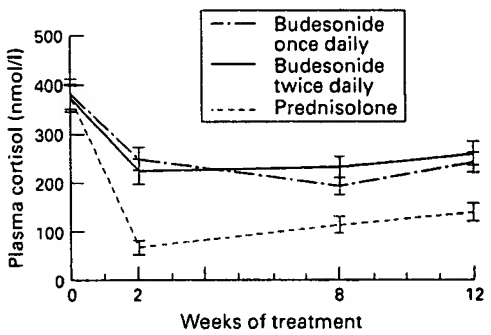

Figure 3: Mean (SE) morning plasma cortisol at randomisation and after two, four, eight, and 12 weeks of treatment with budesonide or prednisolone.

TABLE 2 *Adrenal function (short ACTH test) before and after treatment*

Treatment	At randomisation (%)	After 8 weeks (%)	Comparisons after 8 weeks
Budesonide once daily	86	42	p = 0.55*
			p = 0.013†
Budesonide twice daily	90	50	p = 0.0015‡
Prednisolone	95	16	

*Versus budesonide twice daily; †versus prednisolone; ‡versus prednisolone.

the prednisolone group compared with both budesonide groups. After eight weeks, 76% of prednisolone treated patients had plasma cortisol values below 150 nmol/l compared with 41% in the budesonide once daily group (p=0.0004) and 36% in the budesonide twice daily group (p<0.0001).

Analysis of adrenal function (short ACTH test) revealed statistically significant differences between the groups at eight weeks (p=0.0023) (table 2). After eight weeks, the proportion of patients with normal adrenal function was reduced in all three groups. The maximum reduction was found in the prednisolone group, the difference versus both budesonide once daily (p=0.013) and budesonide twice daily (p=0.0015) being significant. There was no significant difference between the two budesonide groups in this respect.

Glucocorticoid associated side effects

The proportion of patients with glucocorticoid associated side effects was not significantly different between the three groups: 50% in the budesonide once daily group, 44% in the budesonide twice daily group, and 59% in the prednisolone group. However, the number of patients with moon faces found in the prednisolone group was approximately three times higher than in the budesonide groups (p=0.0005). The difference between the groups with respect to other GCS associated side effects was also significant (p=0.0098). Table 3 presents a summary of side effects.

Discussion

Although corticosteroid therapy represents the keystone approach for treating patients with active Crohn's disease, its therapeutic value is counterbalanced by a number of side effects related to systemic activity and to suppression of endogenous adrenal function with associated long term problems and, rarely, idiosyncratic or allergic reactions. The possibility of using a second generation of corticosteroids with comparable efficacy but with fewer side effects offers the prospect of a safer therapy.

TABLE 3 *Glucocorticoid associated side effects*

Sign	Budesonide once daily		Budesonide twice daily		Prednisolone	
	Before study	During study	Before study	During study	Before study	During study
Moon face	1	8	2	7	2	22
Acne	1	12	6	11	–	11
Swollen ankles	–	5	–	2	–	3
Bruises easily	5	7	4	10	2	7
Hirsutism	1	3	1	3	2	3
Buffalo hump	–	–	–	–	–	2
Skin striae	–	–	1	–	–	–
Others*	–	4	–	9	1	16

Some patients experienced more than one glucocorticocoid associated side effect.
*Symptoms considered by the investigator to be signs of possible adverse effects were: weight increase, sweating, dyspepsia, nausea, stiff joints, headache, depression, insomnia, weakness, irritated facial skin, mood swings, limb discomfort, hot flushes, sleep disorder, impaired healing, localised papules, mentally stimulated, cramps in calves, agitation, irritability, emotional lability, generalised oedema, palpitations, localised erythema, facial oedema, and epigastric pain.

Budesonide was shown to be active when given in rectal enemas to patients with ulcerative colitis. An early study showed that it was better than placebo, and other trials have demonstrated that it was comparable to prednisolone in its efficacy but with significantly less action on the pituitary adrenal axis.[4 7–9] The CIR formulation was devised to treat patients with active Crohn's disease localised to the ileum or the ascending colon[10] and the value of this formulation has been tested in two trials.[12 13] A placebo controlled dose finding study[12] suggested that 9 mg daily (4.5 mg twice daily) is the minimal effective dosage of budesonide. In the second study,[13] budesonide 9 mg once daily was as effective as prednisolone 40 mg once daily in inducing remission; at eight weeks, 52% of patients in the budesonide group were in remission compared with 65% in the prednisolone group (p=0.12). The purpose of the present study was, therefore, to compare the two different dose regimens of budesonide CIR therapy—a single morning dose versus a twice daily dosage—and these two approaches were again compared with the standard prednisolone regimen of 40 mg daily, with special reference to efficacy and effects on adrenal axis function. After two weeks of treatment, no significant differences in clinical response were observed between the prednisolone and budesonide once daily groups but fewer remissions were observed in the budesonide twice daily group. After eight weeks, equal remission rates were obtained in the prednisolone and budesonide once daily groups and a somewhat lower remission rate with budesonide twice daily.

The CDAI scores for patients on prednisolone or budesonide once daily decreased in a similar fashion, with a less rapid decline in the budesonide twice daily group. As one of the first aims in treating patients with inflammatory bowel disease is the prompt disappearance of symptoms, this goal was most clearly achieved with budesonide once daily and prednisolone within the first two weeks. These results confirm that budesonide 9 mg daily, given as a single morning dose, is as effective as 40 mg prednisolone, as indicated in the previous study.[13] As we found that budesonide was associated with much less impairment of adrenal axis function, this treatment may well represent the first choice for the management of patients with active Crohn's disease.

Patients with CDAI >300 showed generally a weaker response to treatment compared with those with CDAI <300. In the former group, a higher remission rate was obtained with prednisolone compared with the two budesonide treatments (54%, 31%, and 17% respectively). This trend is not statistically significant (p=0.07) but it might indicate that corticosteroids with systemic effects have a specific role in the treatment of the most severe cases of Crohn's disease. However, even in this subgroup, budesonide would be an important

alternative for patients in whom systemically active steroids should be avoided, such as diabetics.

In the previous comparative study of budesonide 9 mg daily versus prednisolone 40 mg daily, CDAI remission rates at two, four, and eight weeks always favoured prednisolone, and were significant at four weeks (67% *v* 40%, $p<0.001$).[11] However, in the present study, the highest remission rate occurred with budesonide once daily after two weeks; at eight weeks, budesonide once daily did as well as prednisolone. It is difficult to explain the difference between our findings and those of the previous study. There was no substantial difference in severity of the study groups as judged by CDAI scores, and in both studies a single morning dose of budesonide was used. With regard to the different rates of remission observed in the budesonide once daily and the budesonide twice daily groups, it seems that a pulsed dosage regimen produces a more powerful effect.[18 19] As a once daily approach is the most practical and acceptable way to administer a drug to patients and may achieve better compliance, the single morning administration can be recommended. Evidence of adrenal axis suppression was significantly greater in the prednisolone treated patients than in budesonide treated patients. Prednisolone treated patients also showed significant increases in peripheral leucocyte counts and other effects associated with the systemic action of corticosteroids. The conclusions of our multicentre trial are:

- Budesonide CIR, administered as a single daily dosage of 9 mg daily or 4.5 mg twice daily, is comparable to prednisolone for the induction of remission in patients with active Crohn's disease.
- The single morning administration of budesonide CIR is as promptly effective as prednisolone and represents a simpler and safer therapeutic approach, with a reduction in side effects.[20]
- Budesonide CIR offers a useful advance in the treatment of active Crohn's disease while we await a new breakthrough in the therapy of this challenging disease.[21]

Appendix

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